

NDA 16-979/S-048

NOV 15 1999

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

Attention: Joseph A. Linkewich, Pharm.D.
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

Dear Dr. Linkewich:

Please refer to your supplemental new drug application dated July 15, 1998, received July 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MEGACE® (megestrol acetate tablets, USP).

We acknowledge receipt of your amendment dated September 29, 1999.

We note that this supplement was submitted as a Special Supplement .Changes Being Effected under 21 CFR 314.70(c). This supplemental new drug application provides for the following revisions.

1. The deletion of the statement "CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION" and insertion of "Rx only" statement have been made.
2. In the **ADVERSE REACTIONS** section, **Other Adverse Reactions** subsection, "malaise, asthenia, lethargy" have been added to the listing of other adverse reactions that occur.
3. Editorial corrections have been made, for example, gonadetropin to gonadotropin, and the addition of the ® symbol to the places where MEGACE® (megestrol acetate tablets, USP) appears.

Your submission stated October 1, 1998 as the implementation date for the changes.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted July 15, 1998). Accordingly, the supplemental application is approved effective on the date of this letter. However, we request that you make one revision at the next printing of the package insert as follows.

In the **ADVERSE REACTIONS** section, **Glucocorticoid Effects** subsection, the wording should be revised to read “(See **WARNINGS** section.)”.

If a letter communicating important information about this drug product (i.e., a “Dear Health Care Practitioner” letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Leslie Vaccari, Project Manager, at (301) 594-5784.

Sincerely,

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Rx only

MEGACE®

(megestrol acetate tablets, USP)

WARNING

THE USE OF MEGACE® DURING THE FIRST 4 MONTHS OF PREGNANCY IS NOT RECOMMENDED.

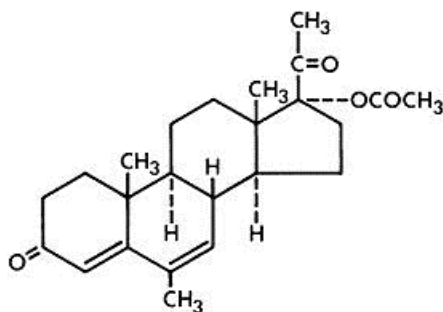
Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion. There is no adequate evidence that such use is effective when such drugs are given during the first 4 months of pregnancy. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first 4 months of pregnancy is not recommended.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female fetus, and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy.

If the patient is exposed to MEGACE during the first 4 months of pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

DESCRIPTION

MEGACE® (megestrol acetate tablets, USP) is a synthetic, antineoplastic and progestational drug. Megestrol acetate is a white, crystalline solid chemically designated as 17(alpha)-acetyloxy-6-methylpregna-4,6-diene-3, 20-dione. Solubility at 37°C in water is 2 mcg per mL, solubility in plasma is 24 mcg per mL. Its molecular weight is 384.51. The empirical formula is $C_{24}H_{32}O_4$ and the structural formula is represented as follows:



megestrol acetate, USP

MEGACE is supplied as tablets for oral administration containing 20 mg and 40 mg megestrol acetate.

MEGACE Tablets contain the following inactive ingredients: acacia, calcium phosphate, FD&C Blue No. 1 Aluminum Lake, lactose, magnesium stearate, silicon dioxide colloidal, and starch.

CLINICAL PHARMACOLOGY

While the precise mechanism by which MEGACE produces its antineoplastic effects against endometrial carcinoma is unknown at the present time, inhibition of pituitary gonadotropin production and resultant decrease in estrogen secretion may be factors. There is evidence to suggest a local effect as a result of the marked changes brought about by the direct instillation of progestational agents into the endometrial cavity. The antineoplastic action of megestrol acetate on carcinoma of the breast is effected by modifying the action of other steroid hormones and by exerting a direct cytotoxic effect on tumor cells.¹ In metastatic cancer, hormone receptors may be present in some tissues but not others. The receptor mechanism is a cyclic process whereby estrogen produced by the ovaries enters the target cell, forms a complex with cytoplasmic receptor and is transported into the cell nucleus. There it induces gene transcription and leads to the alteration of normal cell functions. Pharmacologic doses of megestrol acetate not only decrease the number of hormone-dependent human breast cancer cells but also is capable of modifying and abolishing the stimulatory effects of estrogen on these cells. It has been suggested² that progestins may inhibit in one of two ways: by interfering with either the stability, availability, or turnover of the estrogen receptor complex in its interaction with genes or in conjunction with the progestin receptor complex, by interacting directly with the genome to turn off specific estrogen-responsive genes.

There are several analytical methods used to estimate MEGACE plasma levels, including mass fragmentography, gas chromatography (GC), high pressure liquid chromatography (HPLC), and radioimmunoassay. The plasma levels by HPLC assay or radioimmunoassay methods are about one-sixth those obtained by the GC method. The plasma levels are dependent not only on the method used, but also on intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, intestinal bacteria, antibiotics administered, body weight, diet, and liver function.^{3,4}

Metabolites account for only 5 to 8% of the administered dose and are considered negligible.⁵ The major route of drug elimination in humans is the urine.

When radiolabeled megestrol acetate was administered to humans in doses of 4 to 90 mg, the urinary excretion within 10 days ranged from 56.5 to 78.4% (mean 66.4%) and fecal excretion ranged from 7.7 to 30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1 and 94.7% (mean 86.2%). Respiratory excretion as labeled carbon dioxide and fat storage may have accounted for at least part of the radioactivity not found in the urine and feces.

In normal male volunteers (n=23) who received 160 mg of megestrol acetate given as a 40 mg qid regimen, the oral absorption of MEGACE (megestrol acetate tablets, USP) appeared to be variable. Plasma levels were assayed by a high pressure liquid chromatographic (HPLC) procedure. Peak drug levels for the first 40 mg dose ranged from 10 to 56 ng/mL (mean 27.6 ng/mL) and the times to peak concentrations ranged from 1.0 to 3.0 hours (mean 2.2 hours). Plasma elimination half-life ranged from 13.0 to 104.9 hours (mean 34.2 hours). The steady state plasma concentrations for a 40 mg qid regimen have not been established.

INDICATIONS AND USAGE

MEGACE (megestrol acetate tablets, USP) is indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e., recurrent, inoperable, or metastatic disease). It should not be used in lieu of currently accepted procedures such as surgery, radiation, or chemotherapy.

CONTRAINDICATIONS

History of hypersensitivity to megestrol acetate or any component of the formulation. As a diagnostic test for pregnancy.

WARNINGS

Megestrol acetate may cause fetal harm when administered to a pregnant woman. Fertility and reproduction studies with high doses of megestrol acetate have shown a reversible feminizing effect on some male rat fetuses.⁶ There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

The use of MEGACE in other types of neoplastic disease is not recommended. (See also **PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility** subsection.)

Although the glucocorticoid activity of MEGACE tablets has not been fully evaluated, laboratory evidence of adrenal suppression has been observed. Clinical cases of new onset diabetes, exacerbation of pre-existing diabetes, and Cushing's syndrome have been reported in association with the use of MEGACE. Rare cases of clinically apparent adrenal insufficiency have also been reported in association with MEGACE. The possibility of adrenal suppression should be considered in any patient taking or withdrawing from chronic MEGACE therapy who presents with symptoms of adrenal insufficiency such as hypotension, nausea, vomiting, dizziness, or weakness. Laboratory evaluation for adrenal insufficiency and replacement stress doses of a rapidly acting glucocorticoid may be indicated for such patients.

PRECAUTIONS

General: Close surveillance is indicated for any patient treated for recurrent or metastatic cancer. Use with caution in patients with a history of thromboembolic disease.

Use in Diabetics: Exacerbation of pre-existing diabetes with increased insulin requirements has been reported in association with the use of MEGACE.

Information for the Patients: Patients using megestrol acetate should receive the following instructions:

1. This medication is to be used as directed by the physician.
2. Report any adverse reaction experiences while taking this medication.

Laboratory Tests: Breast malignancies in which estrogen and/or progesterone receptors are positive are more likely to respond to MEGACE.^{7, 8, 9}

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Administration of megestrol acetate to female dogs for up to 7 years is associated with an increased incidence of both benign and malignant tumors of the breast.¹⁰ Comparable studies in rats and studies in monkeys are not associated with an increased incidence of tumors. The relationship of the dog tumors to humans is unknown but should be considered in assessing the benefit-to-risk ratio when prescribing MEGACE and in surveillance of patients on therapy.^{10,11} (See **WARNINGS** section.)

Pregnancy: Pregnancy "Category D". (See **WARNINGS** section.)

Nursing Mothers: Because of the potential for adverse effects on the newborn, nursing should be discontinued if MEGACE is required for treatment of cancer.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Weight Gain: Weight gain is a frequent side effect of MEGACE.^{12,13} This gain has been associated with increased appetite and is not necessarily associated with fluid retention.

Thromboembolic Phenomena: Thromboembolic phenomena including thrombophlebitis and pulmonary embolism (in some cases fatal) have been reported.

Glucocorticoid Effects: (See **WARNINGS** and **PRECAUTIONS** sections.)

Other Adverse Reactions: Heart failure, nausea and vomiting, edema, breakthrough menstrual bleeding, dyspnea, tumor flare (with or without hypercalcemia), hyperglycemia, glucose intolerance, alopecia, hypertension, carpal tunnel syndrome, mood changes, hot flashes, malaise, asthenia, lethargy, sweating and rash.

OVERDOSAGE

No serious unexpected side effects have resulted from studies involving MEGACE administered in dosages as high as 1600 mg/day. Oral administration of large, single doses of megestrol acetate (5 g/kg) did not produce toxic effects in mice.⁶ Megestrol acetate has not been tested for dialyzability; however, due to its low solubility it is postulated that this would not be an effective means of treating overdose.

DOSAGE AND ADMINISTRATION

Breast Cancer: 160 mg/day (40 mg q.i.d.).

Endometrial Carcinoma: 40 to 320 mg/day in divided doses.

At least 2 months of continuous treatment is considered an adequate period for determining the efficacy of MEGACE (megestrol acetate tablets, USP).

HOW SUPPLIED

MEGACE® (megestrol acetate tablets, USP) is available as light blue, scored tablets containing 20 mg or 40 mg megestrol acetate.

NDC 0015-0595-01 20 mg tablet, bottles of 100

NDC 0015-0596-41 40 mg tablet, bottles of 100

NDC 0015-0596-45 40 mg tablet, bottles of 500

NDC 0015-0596-46 40 mg tablet, bottles of 250

STORAGE

Store MEGACE (megestrol acetate tablets, USP) at room temperature; protect from temperatures above 40°C (104°F).

SPECIAL HANDLING

Health Hazard Data

There is no threshold limit value established by OSHA, NIOSH, or ACGIH.

Exposure or "overdose" at levels approaching recommended dosing levels could result in side effects described above (see **WARNINGS** and **ADVERSE REACTIONS** sections). Women at risk of pregnancy should avoid such exposure.

REFERENCES

1. Allegra JC, Kiefer SM: Mechanisms of Action of Progestational Agents. *Semin Oncol* 1985; 12(Suppl 1):3.
2. DeSombre ER, Kuivanen PC: Progestin Modulation of Estrogen-Dependent Marker Protein Synthesis in the Endometrium. *Semin Oncol* 1985; 12(Suppl 1):6.
3. Alexieva-Figus J, et al: Treatment of Metastatic Breast Cancer Patients with Different Dosages of Megestrol Acetate: Dose Relations, Metabolic and Endocrine Effects. *Eur J Cancer Clin Oncol* 1984; 20:33-40.
4. Gaver RC, et al: Liquid Chromatographic Procedure for the Quantitative Analysis of Megestrol Acetate in Human Plasma. *J Pharm Sci* 1985; 74:664.
5. Cooper JM, Kellie AE: The Metabolism of Megestrol Acetate (17-alpha-acetoxy-6-methylpregna-4,6-diene-3, 20-dione) in Women. *Steroids* 1968;11:133.
6. David A, et al: Anti-Ovulatory and Other Biological Properties of Megestrol Acetate. *J Reprod Fertil* 1963; 5:331.
7. McGuire WL, Clark GM: The Prognostic Role of Progesterone Receptors in Human Breast Cancer. *Semin Oncol* 1983; 10(suppl 4):2.
8. Horwitz KB: The Central Role of Progesterone Receptors and Progestational Agents in the Management and Treatment of Breast Cancer. *Semin Oncol* 1988; 15(Suppl 1):14.
9. Bonomi P, et al: Primary Hormonal Therapy of Advanced Breast Cancer with Megestrol Acetate: Predictive Value of Estrogen Receptor and Progesterone Receptor Levels. *Semin Oncol* 1985; 12(Suppl 1):48-54.
10. Nelson LW, et al: Mammary Nodules in Dogs During Four Years' Treatment with Megestrol Acetate or Chlormadinone Acetate. *J Natl Cancer Inst* 1973; 51:1303.
11. Owen LN, Briggs MH: Contraceptive Steroid Toxicology in the Beagle Dog and its Relevance to Human Carcinogenicity. *Curr Med Res Opin* 1976; 4:309.
12. Ansfield FJ, et al: Clinical Results with Megestrol Acetate in Patients with Advanced Carcinoma of the Breast. *Surg Gynecol Obstet* 1982; 155:888.
13. Alexieva-Figus J, et al: Progestin Therapy in Advanced Breast Cancer: Megestrol Acetate--An Evaluation of 160 Treated Cases. *Cancer* 1980; 46:2369.

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